REMARKS

With this amendment, claims 1 and 5-9 are pending. Applicants thank the Examiner for withdrawing the rejections under 35 U.S.C. §112 second paragraph, under 35 U.S.C. §102(b), and under 35 U.S.C. §103(a). For convenience, the Examiner's rejections are addressed in the order presented in the February 5, 2003 Office Action.

Rejections under 35 U.S.C. §103(a)

Claims 1 and 5-9 are rejected under 35 U.S.C. 103(a) as allegedly obvious over Laursen *et al.* (U.S. Patent No. 6,281,336) in view of Flaa *et al.* (U.S. Patent 6,165,336). In response, Applicants respectfully traverse the rejection.

Laursen *et al.* teach a method of producing *total IgG immunoglobulins* (*i.e.*, IgG immunoglobulins that have not been fractionated into subtypes) using anion and cation exchange resins. Flaa *et al.* teach solutions for stabilizing proteins, which, in some embodiments, include sugars, such as lactose, as bulking agents.

In contrast, the claimed invention is a method of manufacturing *IgG4 immunoglobulin subtype*, free of IgG1, IgG2 and IgG3 subtypes for the treatment of diseases and conditions, including serious insect sting allergies. The present inventors, recognizing the importance of preparing pure and clinically effective IgG4 preparations, found for the first time that conventional ion exchange chromatography can be optimized for the preparation of pure IgG4 suitable for injection into allergic individuals. The IgG4 pure preparations prepared from the methods of the present invention contain less protein and more blocking antibody per unit weight, thereby conferring immunity in patients while reducing the risks of aggregation and fragmentation of the immunoglobulin.

Applicants assert that the Office Action fails to establish a *prima facie* case of obviousness. M.P.E.P. § 2143 states the following:

> "[t]o establish a *prima facie* case of obviousness, *three* basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally

> available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. Applicants assert that a *prima facie* case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the references; 2) there is no reasonable expectation of success; and 3) the cited art references do not teach or suggest all the claim limitations.

A. The cited art references do not teach or suggest all the claim limitations.

In order to establish a *prima facie* case of obviousness, the cited art references, alone or in combination, must teach or suggest all the claim limitations. The cited art references do not teach or suggest all the claim limitations, either alone or in combination.

The Office Action alleges that Laursen *et al.* teach a method of producing IgG4 using cation and anion exchange columns. However, Laursen *et al.* teach only a method of purifying *total IgG* from clarified serum, not a method of purifying the *specific IgG4 subtype*.

The Office Action uses Example 2 of Laursen *et al.* in support of IgG subtype purification. After reviewing Example 2 of Laursen *et al.*, Applicants are unable to find any teaching of purification of IgG subtypes, including IgG4. The Office Action appears to refer to a table that analyzes the IgG subclass distribution found in the product of Laursen *et al.*, *i.e.*, the total IgG immunoglobulin fraction. Applicants respectfully point out that Laursen *et al.* disclose the analytic method used to determine the subclass distribution at column 20, lines 6-16, *i.e.*, an immunodiffusion technique.

Immunodiffusion is an assay for quantitation of an antibody, not a purification technique. Thus, Laursen *et al.* teach only how to analyze an IgG immunoglobulin fraction, not how to purify specific IgG subtypes from such a fraction or from serum.

The results of Laursen *et al.* indicate that the ion-exchange purified IgG product contains IgG subtypes in the ratios found in normal human serum, *i.e.*, the IgG subtypes are not separated from one another in the Laursen product. Using the first column of the table as an example, the IgG product of Laursen *et al.* contains 60% IgG1, 35.8% IgG2, 3.5% IgG3, and 0.7% IgG4. Thus, the ion exchange chromatography techniques disclosed in Laursen *et al.* produce a *total IgG fraction* containing all IgG subtypes, not an *IgG4 fraction* that is essentially free of other IgG subtypes as is claimed.

Flaa *et al.* teach only solutions for stabilizing purified proteins and do not teach any methods for purifying proteins, including immunoglobulins. The Office Action also cited Rhodes *et al.* as being relevant to the rejection. However, Rhodes *et al.* teach only methods of radiolabeling antibodies and storage of frozen antibodies. Rhodes does not teach using conventional chromatography techniques to purify IgG4 immunoglobulins.

Thus, alone or in combination, the cited references do not teach or suggest all the claim elements, *i.e.* a method of producing an IgG4 fraction that is essentially free of other IgG subtypes.

B. The cited references do not provide a suggestion or motivation to modify the references, or a reasonable expectation of success in doing so.

In order to establish a *prima facie* case of obviousness, the cited art references, alone or in combination, must provide a suggestion or motivation to modify the references, or a reasonable expectation of success in doing so. The cited art references do not do so.

As described above, Laursen *et al.* does not teach or suggest the use of exchange resins to prepare *IgG4 pure preparations*, rather, the purification procedure taught in Laursen *et al.* relies on buffers having a pH and ionic strength sufficient for the

elution of *total IgG* from the cation exchange resin. Laursen *et al.* does not teach or disclose any purification or separation of IgG subtypes. In contrast, the exchange resins used in the present methods are optimized for elution of pure *IgG4 subtype* from the cation exchange resin. Because the art of fractionation and ion exchange chromatography is unpredictable, one of skill in the art would not expect a purification system for the extraction of pure IgG from crude plasma to be relevant for the purification of an IgG4 subtype from IgG. Therefore, one of skill in the art would not predict that a purification scheme effective for the purification of IgG from crude plasma would be equally effective, or even marginally effective, for the purification of an immunoglobulin subtype IgG4 from an IgG preparation or even the same crude plasma starting material. The Laursen *et al.* patent does not imply otherwise and thus does not provide either a motivation to modify the references or a reasonable expectation of success in doing so.

As discussed above, neither Flaa *et al.* nor Rhodes *et al.* provide any disclosure of purification of specific immunoglobulins or immunoglobulin subtypes. Thus, neither Flaa *et al.* nor Rhodes *et al.* provide a motivation to modify the references to arrive at the claimed invention or a reasonable expectation of success in doing so.

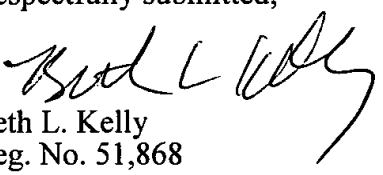
Because the Office Action failed to establish a *prima facie* case of obviousness, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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